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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,936	11/21/2001	Kevin S. Brandt	FC-6-C4	7792

26949 7590 07/29/2004

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EXAMINER	
STRZELECKA, TERESA E	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,936	BRANDT ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-38 and 48-53* is/are pending in the application.

4a) Of the above claim(s) *34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-33 and 48-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed May 24, 2004. Claims 27-38 were previously pending, with claims 34-36 withdrawn from consideration. Applicants cancelled claims 27 and 28, amended claims 29-33 and 37, and added new claims 48-53. Claims 29-38 and 48-53 are pending, with claims 34-36 withdrawn from consideration. Claims 29-38 and 48-53 will be examined.

2. Applicants' amendments and claim cancellations overcame the rejection of claims 27-33, 37 and 38 under 35 U.S.C. 112, first paragraph. However, the amendments introduced new grounds for rejection which will be discussed with respect to Applicants' arguments in the "Response to Arguments" section below. All other rejections are maintained for reasons given below.

Response to Arguments

3. Applicant's arguments filed May 24, 2004 have been fully considered but they are not persuasive.

Regarding the rejection of claims 27-33, 37 and 38 under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph, Applicants main arguments are:

a) Applicants provided alignments of protein sequences with 40 proteins which are characterized as chloride channel proteins, therefore proving the function of the protein. Applicants do not state that the alignment was with SEQ ID NO: 1873. However, it is assumed in a further discussion that this was the sequence Applicants used for homology searches.

b) The amended claim 29 does not lack adequate written description, because "...the specification describes two nucleic acid that encode protein sequence SEQ ID N0:1873 and variants thereof where such variants are highly structurally related to the claimed nucleic acid molecules in

that they must possess at least 95% sequence identity and must be sufficiently similar structurally to possess the same activity."

Regarding a), Applicants provided only alignments and accession numbers of the proteins, without relevant publication dates. Examination of three of these sequences, with accession No. XP_309131.1, NP_572928 and Q9NZA1 revealed the following facts:

i) protein sequence with accession No. XP_309131.1 was published September 17, 2003, was obtained from Anopheles gambiae (mosquito), is incomplete at the N-terminal end, and has no references which would indicate its function,

ii) protein sequence with accession No. NP_572928 was published on April 12, 2004, obtained from Drosophila melanogaster, and does not contain any references to its function,

iii) protein sequence with accession No. Q9NZA1 was published on March 15, 2004, is a human protein named chloride intracellular channel 5. As can be seen from the title of the reference cited, this protein is associated with the actin cytoskeleton of placental microvilli, hardly relevant to fleas.

In principle, these three database entries have been published three of four years after Applicants' filing date. However, even if this evidence was to be admitted, what is a utility of a "chloride channel"? Chloride channels are found in every organism, cell and tissue, and have extremely diverse range of functions. As taught by Jentsch et al. (BioEssays, vol. 19, pp. 117-125),

"Their physiological tasks range from cell volume regulation to stabilization of the membrane potential, signal transduction, transepithelial transport and acidification of intracellular organelles. These different functions require the presence of many distinct chloride channels, which are differentially expressed and regulated by various stimuli. These include various intracellular

messengers (like calcium and cyclic AMP), pH, extracellular ligands and transmembrane voltage." (Abstract). Jentsch et al. further teach that chloride transporters differ in structure and function, and include passive chloride ion transporters, but also cotransporters which couple chloride transport to transport of other ions, such as sodium, potassium, protons (Fig. 1). Jentsch et al. further state:

"Although their ultimate function is similar (providing a pathway for the passive diffusion of anions), this diversity in function could most easily be achieved by the evolution of many distinct Cl^- channels (encoded by different genes). This is now being confirmed by molecular cloning, but a bewildering variety of different Cl^- channels had already been demonstrated by electrophysiological studies. These differ in their biophysical properties (e.g. conductance, ion selectivity, voltage-dependence), their mode of regulation (e.g. by ligands, calcium, G-proteins, etc.) and the tissues in which they have been found." (page 119, fourth paragraph).

The overall picture presented by this review is of enormous variety and complexity of functions and structures, which means that a statement that a protein has "chloride channel" activity does not describe either its structure or its function.

Therefore, Applicants evidence and disclosure are insufficient to provide a specific functional description of the protein with amino acid sequence of SEQ ID NO: 1873.

Regarding b), the issue of the functional annotation of being a chloride channel was discussed above. Further, let us consider a protein which is 95% identical to a protein comprising amino acid sequence of SEQ ID NO: 1873, which has 262 amino acids. That means that at least 13 amino acids of that claimed protein are different. With 21 amino acids to choose from for every of the 13 positions, the number of the claimed proteins is at least 13^{21}, since there is no functional restriction. Further, Applicants do not claim the protein itself, but an isolated nucleic acid encoding a protein which is 95% identical to a protein comprising amino acid sequence of SEQ ID NO: 1873.

Nucleic acid encoding SEQ ID NO: 1373 has 786 bp, a nucleic acid encoding a protein which is 95% identical to a protein comprising amino acid sequence of SEQ ID NO: 1873 would have at least 40 bp different from the nucleic acid encoding SEQ ID NO: 1873, and that is not taking into account the degeneracy of the genetic code. Since each of these bases can have four different possibilities, that gives at least 40^4 different nucleic acids (at least about 2.5 million), out of which Applicants described four. Therefore, there is hardly any question that Applicants did not describe a representative number of species for the entire genus of claimed nucleic acids.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 29-33, 37, 38 and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID NOs: 1872 and 1874-1876. Thus, applicant has express possession of only four particular nucleic acids which encode a protein consisting of amino acid sequence of SEQ ID NO: 1873, in a genus which comprises hundreds of millions of different possibilities. Let us consider a protein which is 95% identical to a protein comprising amino acid sequence of SEQ ID NO: 1873, which has 262 amino acids. That means that at least 13 amino acids of that claimed protein are different. With 21 amino acids to choose from for every of the 13 positions, the number of the claimed proteins is at least 13^{21}. Further, Applicants do not claim the protein itself, but an isolated nucleic acid encoding a protein which is 95% identical to a protein comprising amino acid sequence of SEQ ID NO: 1873. Nucleic acid encoding SEQ ID NO: 1373 has 786 bp, a nucleic acid encoding a protein which is 95% identical to a protein comprising amino acid sequence of SEQ ID NO: 1873 would have at least 40 bp different from the nucleic acid encoding SEQ ID NO: 1873, and that is not taking into account the degeneracy of the genetic code. Since each of these bases can have four different possibilities, that gives at least 40^4 different nucleic acids (at least about 2.5 million), out of which Applicants described four.

Applicants added the limitation of the protein having a chloride channel activity. However, this is not either a functional or structural limitation, as shown by Jentsch et al. (BioEssays, vol. 19, pp. 117-125), who state

"Chloride channels are probably found in every cell, from bacteria to mammals. Their physiological tasks range from cell volume regulation to stabilization of the membrane potential, signal transduction, transepithelial transport and acidification of intracellular organelles. These

different functions require the presence of many distinct chloride channels, which are differentially expressed and regulated by various stimuli. These include various intracellular messengers (like calcium and cyclic AMP), pH, extracellular ligands and transmembrane voltage." (Abstract). Jentsch et al. further teach that chloride transporters differ in structure and function, and include passive chloride ion transporters, but also cotransporters which couple chloride transport to transport of other ions, such as sodium, potassium, protons (Fig. 1). Jentsch et al. further state:

"Although their ultimate function is similar (providing a pathway for the passive diffusion of anions), this diversity in function could most easily be achieved by the evolution of many distinct Cl^- channels (encoded by different genes). This is now being confirmed by molecular cloning, but a bewildering variety of different Cl^- channels had already been demonstrated by electrophysiological studies. These differ in their biophysical properties (e.g. conductance, ion selectivity, voltage-dependence), their mode of regulation (e.g. by ligands, calcium, G-proteins, etc.) and the tissues in which they have been found." (page 119, fourth paragraph).

Therefore, the limitation of the protein having a chloride channel activity does not further limit the number of possible species in the claimed genus of nucleic acids.

Further, these claims encompass alternately spliced versions of the proteins, allelic variants including insertions and mutations, inactive precursor proteins which have a removable amino terminal end, and only specific amino acid sequences have been provided. No written description of alleles, of upstream or downstream regions containing additional sequence, or of alternative splice variants has been provided in the specification.

Even though there is a functional limitation of the nucleic acids having a chloride chanel activity, Applicants did not show that SEQ ID NOs: 1872 and 1874-1876 encode a chloride channel. On page 202 of the specification, Applicants assert that SEQ ID NO: 1872 has 37.5 %

identity with Homo sapiens chloride intracellular channel 2 (Accession No. NM001289). However, the sequence search performed at USPTO did not confirm this result. Further, the sequence search revealed that SEQ ID NO: 1875 is 52.5% identical over 236 bp (443-678) to laminin (Accession No. ABZ25018/c) and 52.5% identical over the same 236 bp (443-678) to a human ion channel (Accession No. AAD27280) (see sequence alignment). Therefore, since these two sequence alignment point to two entirely different classes of proteins, it is not clear that any of the SEQ ID NO: 1872 or 1875 encode a chloride channel.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the nucleic acids encoding a protein comprising amino acid sequence of SEQ ID NO: 1873 or a nucleic acid encoding a protein that is at least 95% identical to SEQ ID NO: 1873, lack any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the four specific sequences, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "an isolated nucleic acid molecule that encodes a protein selected from the croun consisting of a protein comprising amino acid sequence SEQ ID N0:1873 and a protein that is at least 95% identical to SEQ ID NO:1873", for example.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as nucleic acid encoding proteins comprising SEQ ID NO: 1873 or proteins with 95% sequence identity to SEQ ID NO: 1873, without any definition of the particular sequences claimed.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which comprise SEQ ID NO: 1872 and 1874-1876. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 48-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 48-53 are indefinite in claim 48. Claim 48 is indefinite over the recitation of "An isolated C. felis cDNA molecule or a C. felis RNA molecule nucleic acid molecule". It is not clear whether there is a third type of a nucleic acid molecule in this claim (see underline).

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 29-33, 37, 38 and 48-53 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of C. felis nucleic acids encoding a protein selected from the group consisting of a protein comprising amino acid sequence SEQ ID NO: 1873 and a protein that is at least 95% identical to SEQ ID NO: 1873, wherein said protein has chloride channel activity.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the nucleic acids. The only cited utilities identified by the examiner are to detect other nucleic acid molecules (page 125, lines 12-22), preparation of oligonucleotides capable of hybridization to the nucleic acids, acting as probes, primers or antisense molecules (page 126, lines 7-20), preparation of recombinant vectors for expression of polypeptides (page 127, lines 3-22) and vaccines (page 148). These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well

established utilities for the protein. No well established utilities for these specific nucleic acids are identified the specification.

Substantial utility

Given the absence of a well established utility, the next issue is whether substantial utilities are disclosed in the specification. Here, the only evidence provided by Applicants is an assertion on page 202 of the specification that SEQ ID NO: 1872 has 37.5 % identity with Homo sapiens chloride intracellular channel 2 (Accession No. NM001289). However, the sequence search performed at USPTO did not confirm this result. Further, the sequence search revealed that SEQ ID NO: 1875 is 52.5% identical over 236 bp (443-678) to laminin (Accession No. ABZ25018/c) and 52.5% identical over the same 236 bp (443-678) to a human ion channel (Accession No. AAD27280) (see sequence alignment). Therefore, since these two sequence alignment point to two entirely different classes of proteins, it is not clear that any of the SEQ ID NO: 1872 or 1875 encode a chloride channel.

Even if this argument was not persuasive, the utility of a protein having an activity of a "chloride channel" is not a substantial utility. As shown by Jentsch et al. (BioEssays, vol. 19, pp. 117-125), there are potentially hundreds of different chloride channels, performing a lot of different functions in different cells and with different structures:

"Chloride channels are probably found in every cell, from bacteria to mammals. Their physiological tasks range from cell volume regulation to stabilization of the membrane potential, signal transduction, transepithelial transport and acidification of intracellular organelles. These different functions require the presence of many distinct chloride channels, which are differentially expressed and regulated by various stimuli. These include various intracellular messengers (like calcium and cyclic AMP), pH, extracellular ligands and transmembrane voltage." (Abstract).

Jentsch et al. further teach that chloride transporters differ in structure and function, and include passive chloride ion transporters, but also co-transporters which couple chloride transport to transport of other ions, such as sodium, potassium, protons (Fig. 1). Jentsch et al. further state:

"Although their ultimate function is similar (providing a pathway for the passive diffusion of anions), this diversity in function could most easily be achieved by the evolution of many distinct Cl^- channels (encoded by different genes). This is now being confirmed by molecular cloning, but a bewildering variety of different Cl^- channels had already been demonstrated by electrophysiological studies. These differ in their biophysical properties (e.g. conductance, ion selectivity, voltage-dependence), their mode of regulation (e.g. by ligands, calcium, G-proteins, etc.) and the tissues in which they have been found." (page 119, fourth paragraph).

Applicants assert in the specification that the nucleic acids encoding chloride channels can be used as targets for anti-flea vaccines and drugs (page 15, lines 8-11). However, Applicants state "If the CLIC gene product is indeed involved in transepithelial chloride transport in HMT tissues..." (page 15, lines 8 and 9), further confirming that Applicants did not know the function of a protein encoded by SEQ ID NO: 1872 or 1875.

Specific Utility

The claimed nucleic acid compounds are not supported by a specific utility because the disclosed uses of the nucleic acids are not specific and are generally applicable to any nucleic acid. The specification states that the nucleic acid compounds may be useful to detect other nucleic acid molecules (page 125, lines 12-22), preparation of oligonucleotides capable of hybridization to the nucleic acids, acting as probes, primers or antisense molecules (page 126, lines 7-20), preparation of recombinant vectors for expression of polypeptides (page 127, lines 3-22) and vaccines (page 148).

These are non-specific uses that are applicable to nucleic acids and proteins in general and not particular or specific to the nucleic acids and proteins being claimed.

10. Claims 29-33, 37, 38 and 48-53 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

11. No references were found teaching or suggesting claims 29-33, 37, 38 and 48-53, but they are rejected for reasons given above.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

TS
July 21, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER